

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cloxacillin Sodium Capsules USP 250 mg (M-CLOX250)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin contains:

Cloxacillin sodium USP Equivalent to Cloxacillin 250 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Size 2, Blue cap and yellow body capsules filled with white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is used in the treatment of infections caused by streptococci when associated with sensitive penicillinase-producing staphylococci; also in the treatment of all staphylococcal infections, whether penicillin G-sensitive or resistant.

In infections suspected of being caused by penicillinase-producing staphylococci, cloxacillin may be used for initial treatment after appropriate specimens have been taken for culture and before results of microbial susceptibility tests are known. If the results of identification and susceptibility tests indicate that the infecting organism is not a penicillinase-producing staphylococcus susceptible to cloxacillin, cloxacillin should be discontinued and treatment with an appropriate alternative agent instituted.

To reduce the development of drug-resistant bacteria and maintain the effectiveness and other antibacterial drugs, Cloxacillin sodium should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility

information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration

Adults:

Mild to moderate infections: 250 to 500 mg every 6 hours. It should be given 1 to 2 hours before meals as the presence of food in the stomach and small intestine reduces absorption. Maintain therapy for a minimum of 5 days.

Larger doses may be required for very severe infections. A daily dose of 6 g should not be exceeded.

Children:

Up to 5 kg (11 lb) body weight: 250mg/day.

Over 5kg(11lb) upto approximately 40kg(85lb) body weight: 50mg/kg/day. Total daily dosage must be divided into 4 doses, 1 dose given every 6 hours.

In infections associated with streptococcus pyogenes, treatment should be continued for at least 10 days to reduce the risk of glomerulonephritis or rheumatic fever.

4.3 Contraindications

Cloxacillin should not be given to patients with a history of penicillin allergy or administered to neonates born of mothers hypersensitive to penicillin.

Patients allergic to cephalosporins may also be allergic to penicillins.

Cloxacillin is incompatible with aminoglycosides, tetracyclines, erythromycin and polymyxin B.

4.4 Special warnings and precautions for use**Warnings:**

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin therapy. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic or anaphylactic reaction occurs, discontinue treatment and administer the usual agents, e.g. antihistamines, pressor amines, corticosteroids.

Safety for use in pregnancy has not been established.

Development of Drug Resistant Bacteria

Prescribing Cloxacillin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Precautions:

Candidiasis and other superinfections may occur, especially in debilitated and malnourished patients, or those with low resistance to infection due to corticosteroids, immunosuppressive agents or irradiation. If superinfection occurs, institute appropriate measures.

During long-term therapy, renal, hepatic and hematopoietic functions should be checked periodically.

Experience in premature and newborn infants is limited. Cautious administration of the drug to such patients and frequent evaluation of organ system function is recommended.

The passage of any penicillin from blood into brain is facilitated by inflamed meninges and during cardiopulmonary bypass. In the presence of such factors, particularly in renal failure when high serum concentrations can be attained, central nervous system adverse effects including myoclonia, convulsive seizures and depressed consciousness can be expected. Although this complication has not been reported with cloxacillin, it should be anticipated.

4.5 Interaction with other medicinal products and other forms of interaction

BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). Avoid combination

BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). Monitor therapy

Methotrexate:Penicillins may increase the serum concentration of Methotrexate. Monitor therapy

Mycophenolate:Penicillins may decrease serum concentrations of the active metabolite(s) of Mycophenolate. This effect appears to be the result of impaired enterohepatic recirculation. Monitor therapy

Probenecid: May increase the serum concentration of Penicillins. Management: Avoid the routine use of penicillins and probenecid, but this combination may be used advantageously in select cases with careful monitoring. Monitor for toxic effects of penicillins if probenecid is initiated or the dose is increased. Consider therapy modification

Sodium Picosulfate: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic. Consider therapy modification

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. Consider therapy modification

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents. Consider therapy modification

Vitamin K Antagonists (eg, warfarin): Cloxacillin may diminish the anticoagulant effect of Vitamin K Antagonists. Cloxacillin may enhance the anticoagulant effect of Vitamin K Antagonists. Monitor therapy

Acute haemolytic anaemia

Care should be taken when administering high doses of cloxacillin especially to patients with impaired renal function as there is a risk of neuro-toxicity and congestive heart failure.

Disturbance of electrolyte balance may occur following administration of large doses. Increases in liver enzyme values have been reported.

Renal and haematological systems should be monitored during prolonged and high dose therapy, patients with syphilis may exhibit the Jarish-Herxheimer reaction and should also therefore be monitored

4.6 Fertility, pregnancy and lactation

Pregnancy

Cloxacillin has been assigned to pregnancy category B. There are no controlled data in human pregnancies; however, there are no literature reports of congenital abnormalities associated

with it. Cloxacillin should only be given during pregnancy when need has been clearly established.

Breastfeeding

There are no data on the excretion of cloxacillin into human milk. Other penicillins are excreted into human milk in small amounts. Adverse effects in the nursing infant are unlikely.

4.7 Effectsonabilitytodriveandusemachines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Gastrointestinal disturbances, such as nausea, vomiting, epigastric discomfort, flatulence and loose stools, have been noted in some patients. Rarely, mild leukopenia has occurred. Mildly elevated SGOT levels (less than 100 units) have been reported in a few patients for whom pre-therapeutic determinations were not made. Fever, anaphylaxis and allergic reactions (rash, urticaria) including wheezing and sneezing, have occasionally been encountered.

Eosinophilia, with or without overt allergic manifestations, has been noted in some patients during therapy. Thrombophlebitis has occurred occasionally I.V. therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

When penicillin reaches a certain (as yet undetermined) concentration in the cerebrospinal fluid, neurotoxic symptoms may occur consisting of myoclonia, convulsive seizures, and depressed consciousness. Unless administration of the drug is stopped or its dosage reduced, the syndrome may progress to coma and death. Penicillin does not normally cross the blood-brain barrier to any substantial extent, but when massive doses are used (several grams a day) in the presence of inflamed meninges and/or impaired renal function, or in elderly patients, the drug may cause the above-mentioned toxic reactions. No antidote is required.

Discontinue medication, induce prompt elimination of unabsorbed drug. Employ supportive measures to control allergic reactions with conventional therapy (i.e., administration of empinephrine corticosteroids, antihistamines) as indicated. In patients with renal function impairment cloxacillin class antibiotics and be removed by hemodialysis but not by peritoneal dialysis.

Treatment of overdose:

Stop administration temporarily - promote excretion (dialysis, etc.). Toxic serum levels and the lethal serum level of cloxacillin in man are not known

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Semisynthetic penicillin antibiotics

ATC code: J01CF02.

Mechanism of action:

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Sodium cloxacillin monohydrate is rapidly but incompletely absorbed from the gastrointestinal tract after oral administration.

When a dose of 500 mg cloxacillin sodium (2 x 250 mg cloxacillin sodium capsules) was administered to fasting adult volunteers, a mean peak plasma level of 8.5 mcg/mL was obtained with a T_{max} of 0.88 hr.

A dose of 500 mg cloxacillin sodium reconstituted granules for oral solution yielded peak plasma levels of 13.3 mcg/mL with a T_{max} of 0.58 hr. in fasting adult volunteers.

Oral doses of 250 mg sodium cloxacillin to adult fasting volunteers resulted in 4.8 mcg/mL peak serum levels with a T_{max} of 1 hr.

Mean urinary excretion of cloxacillin after an oral dose of 500 mg was found to be 37%. Total urinary excretion in healthy volunteers was 62% of an intravenously injected dose of 750 mg (250 mg/hr for three hours).

Food delays the absorption of cloxacillin sodium. Cloxacillin, 9, 10 Sodium cloxacillin is bound to serum proteins to the extent of 94%.

The plasma half-life of cloxacillin is reported to be 25 minutes in healthy volunteers following infusion of 750 mg over a 3 hour period.¹² The plasma half-life in uremic patients was increased to 49 minutes.

Cloxacillin passage across the CNS barrier is insufficient for practical purposes unless the meninges are inflamed. Cloxacillin passes the placental barrier as do the penicillins to the extent of about 50% of the mother's plasma level.

Serum concentrations are enhanced if probenecid is given concomitantly

5.2 Pharmacokinetic properties

Absorption:

Cloxacillin sodium is incompletely absorbed from the gastro intestinal tract after oral administration, and absorption is further reduced by the presence of food in the stomach. After an oral dose of 500 mg, a peak plasma concentration of 7 to 14 µg/ml is obtained in fasting subjects in 1 to 2 hours. Absorption is more complete when given by intramuscular injection and peak plasma concentrations of about 15 µg/ml have been observed 30 minutes after a dose of 500 mg. Doubling the dose can double the plasma concentrations. Oral: ~50%; reduced by food

Distribution:

Widely to most body fluids and bone; penetration into cells, into eye, and across normal meninges is poor; inflammation increases amount that crosses blood-brain barrier.

About 94% of cloxacillin in the circulation is bound to plasma proteins. Cloxacillin has been reported to have a plasma half - life of 0.5 to 1 hour. The half - life is prolonged in neonates. Cloxacillin crosses the placenta and is excreted in breast milk. There is little diffusion into the CSF except when the meninges are inflamed. Therapeutic concentrations can be achieved in pleural and synovial fluids and bone.

Biotransformation:

Metabolised by liver to active and inactive metabolites

Elimination:

Cloxacillin is metabolised to a limited extent, and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 35% of an oral dose is excreted in the urine and upto 10% in the bile.

5.3 Preclinical safety data:

Not applicable

6. PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

- Ethyl cellulose
- Colloidal silicon dioxide
- Acetone
- Talc
- Maize starch
- Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36months.

6.4 Specialprecautionsforstorage

Store in a dry place below 30°C. Protect from light.

6.5 Natureandcontents ofcontainer

PrimaryContainer(s):Cloxacillin sodium Capsules(M-CLOX 250) isavailable in 10x10's, blister pack

SecondaryContainer:

Each Strip packed in a Printed Carton with relevant batch details along withleaflet.

- Carton: ITCCyber XLwithaquavarnishsideopenwith300GSMmulti-colours.
- Leaflet:60GSMMaplithopaper.

OuterContainer:

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labeled with product name and relevant batch details and sealed with BOPP tape. Shippersare then strapped with Polypropylenetapes.

6.6Specialprecautionsfordisposalandotherhandling

Not applicable

7. Marketing authorizationholder

NameandPermanentaddressoftheMarketingauthorizationholder:

Medopharm, Private limited

“MEDOHOUSE”

25, Puliur II Mainroad,Trustpuram, Chennai-600024,

Tamil Nadu,India.

PH: +9144-30149992/30149955

Fax: 260211286283

Manufacturing Siteaddress:

Medopharm Private Limited,

No. 50, Kayarambedu Village,

Guduvanchery-603 202, Tamil Nadu,India.

8. Number (s) in the National register of finished pharmaceutical products

First registration No. MEDO/IND/008 certificate No.: 281/04

Second registration No. MEDO/IND/008 certificate No. R/043/10

Renewal registration - 06297/08042/REN/2021

9. Date of first authorization/renewal of the authorization

First authorization – 18/06/2012

Second authorization - 18.08.2017

Renewal authorization - 25.07.2021

10. Date of revision of the text

13.07.2023